

December 14, 2000

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane -- Room 1061
Rockville MD 20852

Re: Physical Medicine Devices; Revision of the Identification of the
Iontophoresis Device, Docket No. 00N-1409, 65 Fed. Reg. 50949
(August 22, 2000)

COMMENTS OF BIRCH POINT MEDICAL, INC.

Birch Point Medical, Inc. (Birch Point) submits these comments on the proposal published by the Food and Drug Administration (FDA) to revise the identification of iontophoresis devices, 21 C.F.R. § 890.5525. Birch Point Medical is a small business entity that manufactures and markets the LontoPatch, an iontophoresis delivery device recently cleared by FDA through section 510(k) notification procedures.

Class III iontophoresis devices are intended for the delivery of drugs that do not bear labeling describing iontophoresis. In its proposal, FDA claims that it has "discovered" that no iontophoresis devices meeting the Class III description were marketed prior to May 28, 1976. On the claim of this "discovery," FDA proposes to revise the identification of iontophoresis devices in 21 C.F.R. § 890.5525, by deleting the Class III identification for preamendment devices.

As explained below, FDA's proposal is based on a significant factual error. Iontophoresis devices have been marketed for nearly a century for

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general drug delivery -- i.e., for delivery of any ionizable drug the health care professional, in his sole discretion, chooses to administer. Many, perhaps most, of these drugs lacked before 1976 (and continue to lack) labeling that references iontophoresis delivery. FDA's fundamental factual error renders the Agency's proposal arbitrary, capricious, and unlawful under the Administrative Procedure Act, 5 U.S.C. §§ 552 & 706(2). FDA's sole justification for its proposal is the "fact" about which it is mistaken. Accordingly, FDA must rescind the proposal.

In addition, FDA significantly underestimates the economic impact of its proposal on small businesses, in violation of the Regulatory Flexibility Act, 5 U.S.C. § 601 et seq. If FDA were to proceed with this erroneously-based proposal, it would be obliged to reassess the impact of its proposal, consider less burdensome alternatives, and publish a new "Analysis of Impacts."

I. BACKGROUND

A. Scientific Background

Iontophoresis. Iontophoresis is the delivery of medication by means of an electrical current rather than an injection. The drug solution is diluted and ionized; i.e., positively or negatively charged. A bipolar electric field propels the charged molecules across intact skin and into the underlying tissue. The ions are transferred to the body in a rate proportional to the magnitude of the current flow between the electrodes. Iontophoresis is, thus, a noninvasive transdermal drug delivery system. The technology can be used to deliver any small molecule substance that can be ionized; examples include anti-inflammatory drugs such as dexamethasone and anesthetic drugs such as

lidocaine. Iontophoresis reduces the risk of infection and allows drug delivery without the psychological trauma of needle insertion.

Device Design. The Preston Corporation PC 2900 low volt generator is one example of the iontophoresis devices marketed in the middle of the 1900s. Like all iontophoresis devices, it had a positive electrode, a negative electrode, a reservoir associated with each electrode into which positively or negatively charged drug solution could be placed, and a source of low-level electrical current. The source of power in the case of the PC 2900 was a DC generator measuring 10 x 8 x 9.5 inches. An advertisement of the PC 2900, from 1963, is included at Attachment 1. Devices manufactured and marketed in the mid-1900s included the Teca SP-2 and SP-5, the Tomac Mobile Low Volt Generator, J.A. Preston's Galvanic-Faradic-Sinusoidal Generator, the Mark V from Medco, and the Medi-Sine Model 1400MGF from Dallons. (See below pages 18-19, and attachments 1, 9-17.)

Many iontophoresis devices on the market today resemble the Iomed Phoresor, a microprocessor-controlled battery-powered DC current generator with drug delivery electrodes composed of hydrogel material. Birch Point manufactures a disposable single-use device with a self-contained battery source. The entire patch measures 3 x 5 inches, including battery source and both electrodes. Positively charged ions in solution are applied to the patch at the site of the positive electrode, and negatively charged ions in solution are applied to the patch at the site of the negative electrode. (Isotonic saline can be substituted for medication on one side, if medication delivery is only intended

from one electrode.) The patch is applied to the skin and delivers a fixed dosage before automatically shutting off.

Clinical Use. Clinical use of iontophoresis dates to the early 1900s. By 1939, the American Medical Association's Handbook of Physical Therapy included a section on iontophoresis and explained that its practitioners used "constant current to deposit the ions of certain salts in solution on or in tissues."¹ By the early 1970s, over one quarter of the physical therapy centers in the United States used iontophoresis.² In a 1971 study, responding centers indicated they used iontophoresis devices to treat cervical and lower back pain, arthritis, fungus infections, ulcers, bursitis, plantar warts, and skin conditions. They reported using vasodilators (histamine and methacoline), local anesthetics (procaine), drugs that affected skin permeability (hyaluronidase), and astringents (copper sulfate, aluminum chloride).³

Pre-1976 therapeutic uses of iontophoresis in the clinic have included:

- administration of fluoride for reduction of dental hypersensitivity and for cavity prevention;⁴

¹ American Medical Association, Handbook of Physical Therapy 207-09 (3d ed. 1939) (Attachment 2) (hereinafter "AMA Handbook").

² Linda Amrein et al., "Use of Low Voltage Electrotherapy and Electromyography in Physical Therapy," Physical Therapy 51/12: 1283 (1971) (Attachment 3). Amrein sent a questionnaire to 302 physical therapy centers in hospitals and clinics throughout the United States. Of the responding centers, over one fourth (26 percent) indicated that they used iontophoresis.

³ Id.

⁴ See 44 Fed. Reg. 50520, 50522 (August 28, 1979) ("The use of fluoride iontophoresis has a broad application in dental practice.").

- administration of sodium salicylate for the treatment of arthritis, Raynaud's disease, and scleroderma;⁵
- administration of idoxuridine for treatment of herpes labialis;⁶
- administration of methylprednisone succinate for aphthous ulcers;⁷
- administration of magnesium for neuritis and myositis;⁸
- administration of calcium for myospasm;⁹
- administration of copper sulfate for fungal infections;¹⁰
- administration of iodine for fibrositis and adhesions;¹¹
- administration of acetic acid to soften or eliminate calcium deposits;¹²
- administration of lidocaine and dexamethasone for treatment of tendonitis;¹³

⁵ Affidavit of Luther Kloth ¶¶ 3-4 (Attachment 4) (hereafter "Kloth Affidavit").

⁶ School of Dental Medicine, SUNY at Stony Brook, Student Educational Site, Iontophoresis Lecture Slides <www.hsc.sunysb.edu/oralbio/iontohires> (visited September 25, 2000).

⁷ Id.

⁸ Joseph Kahn, Principles and Practice of Electrotherapy 164 (1987) (Attachment 5) (hereafter "Kahn Text").

⁹ Id.; see also October 1998 BioMechanics Roundtable Transcript <www.biomech.com/db_area/archives/1998/9810round.25-29.bio-.html> (visited September 25, 2000) (hereafter "Roundtable Transcript").

¹⁰ Kahn Text, at 164; Affidavit of Neil I. Spielholz ¶ 3 (Attachment 6) (hereafter "Spielholz Affidavit"); Kloth Affidavit ¶¶ 3-4.

¹¹ Kahn Text, at 164.

¹² Id., see also Roundtable Transcript; Kloth Affidavit ¶¶ 3-4.

¹³ Affidavit of Danny D. Smith ¶ 3 (Attachment 7) (hereafter "Smith Affidavit").

- administration of dexamethasone for bursitis, arthritis, and tendonitis;¹⁴
- administration of "ionizing steroids" for tendonitis and bursitis;¹⁵
- administration of sodium chloride for scar tissue;¹⁶ and
- administration of hyaluronidase for edema.¹⁷

To the best of our knowledge, none of these drugs was labeled for use with an iontophoresis device.¹⁸ Indeed, to date FDA has approved only one drug for delivery via iontophoresis: Iontocaine (lidocaine 2%), which was approved on December 21, 1995, for dermal analgesia by iontophoresis.

Iontophoresis also has a diagnostic use, dating to a published clinical study in 1959.¹⁹ Pilocarpine hydrochloride can be administered via iontophoresis in order to induce sweating for the diagnosis of cystic fibrosis. The

¹⁴ Smith Affidavit ¶ 3.

¹⁵ Comments of Clinton L. Compere (September 20, 1979) (Docket No. 78N-1240).

¹⁶ Spielholz Affidavit ¶ 3.

¹⁷ Id.; Kloth Affidavit ¶¶ 3-4.

¹⁸ We are aware that prior to the 1962 Drug Amendments, at least one drug bore labeling that described iontophoresis delivery. Specifically, we have located a 1941 brochure from Merck describing iontophoresis of mecholyl for a variety of indications. Attachment 8. The entries for mecholyl in the 1947 and 1950 editions of the Physician's Desk Reference describe iontophoretic delivery. However, we are not aware of any other drugs as to which this is the case. Also, after the 1962 Drug Amendments, the iontophoresis labeling was omitted for mecholyl. Between the 1962 Drug Amendments and the 1976 Medical Device Amendments, iontophoresis devices were marketed and used for general drug delivery, and the drugs in question were not labeled with directions for use with those devices.

¹⁹ L.E. Gibson & R.E. Cooke, "A test for the concentration of electrolytes in sweat in cystic fibrosis of the pancreas using pilocarpine by electrophoresis," Pediatric 23: 545-549 (1959).

Gibson-Cooke Quantitative Pilocarpine Iontophoresis Sweat Test, QPIT, is now a major tool in the diagnosis of cystic fibrosis.

B. Legal Background

In 1983, FDA issued a final classification rule for iontophoresis devices. 48 Fed. Reg. 53032. That rule defined Class II and Class III iontophoresis devices, with the classification depending on the intended use. FDA now asserts that there were no iontophoresis devices meeting the Class III definition prior to May 28, 1976. Based solely on this assertion, with no factual discussion whatsoever, FDA proposes to revoke the Class III identification. FDA's assertion is factually incorrect, as shown in these comments.

Understanding the significance of FDA's new assertion requires a brief explanation of the device classification system and the amendments to the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 et seq. (FD&C Act), involving medical devices. It also requires a discussion of the history regarding the classification of iontophoresis devices.

1. The 1976 Medical Device Amendments

The device classification system dates to the 1976 Medical Device Amendments to the FD&C Act. Classification of a medical device turns on the perceived risks of the device and the extent to which various regulatory controls will reduce that risk. Class I devices have the least risk and the fewest controls, and Class III the most. All devices in all classes are subject to the general controls in the FD&C Act and corresponding FDA regulations. General controls include requirements for facility registration and product listing with FDA,

adherence to good manufacturing practices, the maintenance of records, and the filing of reports regarding marketing experience.

A Class I device is a device as to which the general controls are sufficient to provide a reasonable assurance of safety and effectiveness.²⁰ A device may also be placed in Class I if there is "insufficient information" as to whether general controls will be sufficient, provided the device (1) is not purported or represented to be for a use in supporting or sustaining human life or for a use which is of substantial importance in preventing impairment of human health, and (2) does not present a potential unreasonable risk of illness or injury.²¹

A Class II device is one (1) that cannot be placed in Class I because general controls by themselves are insufficient to provide a reasonable assurance of the safety and effectiveness of the device, but (2) for which there is sufficient information to establish special controls to provide that assurance.²² Special controls include performance standards, postmarket surveillance, patient registries, and guidelines (e.g., guidelines for the submission of clinical data in a premarket notification submission).

A Class III device is one that is purported or represented to be "for a use in supporting or sustaining life," or "for a use which is of substantial importance in preventing impairment of human health," or one which "presents a

²⁰ 21 C.F.R. § 860.3(c)(1).

²¹ Id.

²² Id. § 860.3(c)(2).

potential unreasonable risk of illness or injury" and the premarket approval process is necessary to provide a reasonable assurance of its safety and effectiveness.²³ A device will also fall in Class III if insufficient information exists to determine that special controls would provide reasonable assurance of the device's safety and effectiveness.²⁴

Devices already available on the market on May 28, 1976, the enactment date of the Amendments, are called "preamendment devices." The 1976 Amendments required FDA to review and classify every preamendment device. A preamendment device that was classified into Class III would be subject to the premarket approval process. However, FDA may not require submission of a premarket approval application (PMA) until 90 days after promulgating a final rule requiring PMAs for the device or 30 months after final classification of the device in Class III, whichever is later. Iontophoresis devices were classified in 1983, but FDA has not yet called for PMAs for the Class III devices. Accordingly, preamendment iontophoresis devices meeting the current Class III identification have been -- and until FDA calls for PMAs must be -- authorized for marketing pursuant to section 510(k) notification procedures.

²³ Id. § 860.3(c)(3).

²⁴ Id.

2. Classification of Iontophoresis Devices

After enactment of the 1976 Amendments, three device classification panels reviewed iontophoresis devices.²⁵ After meeting in February 1978, the Dental Device Classification Panel recommended that iontophoresis devices be classified into Class I for fluoride uptake acceleration.²⁶ After meeting in November 1978, the Ear, Nose, and Throat Device Classification Panel recommended Class II status for iontophoresis devices used with epinephrine and lidocaine to anesthetize the inner ear.²⁷ The transcript of the Physical Medicine Device Classification Panel meeting in July 1978 suggests the panel would have voted to recommend classifying the devices intended for general use into Class II. (Tr. 137, Tr. 137-144.)

In August 1979, FDA issued its proposed classification rule.²⁸ Consistent with the panel recommendations, FDA proposed to place iontophoresis devices in Class II for three specific uses: (1) administration of pilocarpine for diagnosis of cystic fibrosis; (2) administration of lidocaine for anesthesia of the ear canal; and (3) administration of fluoride to the teeth.²⁹

²⁵ Three panels met before FDA issued its proposed rule. Two panel transcripts are available -- from the Physical Medicine Device Classification Panel meeting on July 7, 1978, and from the Ear, Nose, and Throat Device Classification Panel meeting on November 6, 1978.

²⁶ See 44 Fed. Reg. 50520 (August 28, 1979) (proposed rule). We have been unable to locate the transcript of this panel meeting, but the summary minutes are available from the hearing clerk and confirm this vote.

²⁷ M-D-D-I Reports 2 (November 13, 1978).

²⁸ 44 Fed. Reg. 50520 (August 28, 1979)

²⁹ Id. at 50522-50523.

--- Iontophoresis devices for all remaining uses were to be placed in Class III. Premarket approval would be required for "a device used to deliver ions of soluble salts (i.e., medications), by use of a direct current, into the tissues of the body for therapeutic or diagnostic purposes."³⁰

In December 1979, an FDA staff member, Ivana Roberts, summarized the conclusions of these three panels and FDA's proposed rule:

What we did in writing this regulation was to go through all the literature and find uses that had quite a bit of clinical experience, basically, uses that there was no other alternative for that use. And it was safe and effective in those uses. If you read the regulation, we came up with -- for diagnosing cystic fibrosis -- there is really no alternative to using iontophoresis in a solution that ionized it to the skin. It is relatively safe, not harmful. Also, with the iontophoretic fluoride in the teeth. We got that recommendation from the Dental Panel and they had the literature to back that up, that it was safe and effective. Also, for anesthetizing of the tympanic membrane of the ear. We got that from the Ear, Nose, and Throat Panel. They had quite a bit of literature to back them up.³¹

Three comments were filed in the docket. In September 1979, a physician at Northwestern University Medical School filed a comment disagreeing with the Class III status of iontophoresis devices. Dr. Compere specifically noted that he treated tendonitis and bursitis with "an ionizing steroid

³⁰ Id. at 50523.

³¹ Transcript, Physical Medicine Section of the Surgical and Rehabilitation Devices Panel, at 16 (December 12, 1979) (Ivana Roberts).

compound."³² The McGhan Medical Corporation filed comments in October 1979, pointing out that iontophoresis "has been effectively utilized for over a decade in the field of dentistry" and "has been used successfully and harmlessly in the ear under the current procedure since 1973." It objected to the device's placement in Class III for general drug applications.³³ The General Medical Company, the manufacturer of an iontophoresis device for sweat inhibition, filed comments requesting Class II status in November 1979.³⁴ No other comments were filed.

In December 1979, the Physical Medicine Device Section of the Surgical and Rehabilitation Devices Panel met to discuss iontophoresis devices in light of these comments.³⁵ After Ivana Roberts of FDA explained the proposed rule, she explained that remaining uses of the device had been placed in Class III because FDA had identified "hazards" and "problems" with "general drug delivery." (Tr. 17.) In short, FDA believed it lacked evidence of safety and effectiveness of iontophoresis devices for general drug delivery. Nevertheless, in light of the comments filed, it referred the classification question back to the panel. The panel expressed skepticism about the effectiveness (not the safety)

³² Comments of Clinton L. Compere (September 20, 1979) (Docket No. 78N-1249).

³³ Comments of McGhan Corporation (October 5, 1979) (Docket No. 78N-1249).

³⁴ Comments of General Medical Company (November 14, 1979) (Docket No. 78N-1249). FDA would eventually deny a petition to downclassify iontophoresis devices for this use. 49 Fed. Reg. 18789 (May 2, 1984).

³⁵ 44 Fed. Reg. 66065 (November 16, 1979) (announcing meeting to "discuss comments in response to the proposed regulations").

of iontophoresis devices, based on the clinical studies then available. (Tr. 19-22.) The panel voted that iontophoresis devices be placed in Class II for cystic fibrosis diagnosis, application of fluoride to teeth, and application of anesthetics to the tympanic membrane, and that they be placed in Class III for general drug delivery. (Tr. 29.)

In 1983, FDA issued its final rule on the classification of iontophoresis devices.³⁶ Without explanation, it abandoned its 1979 proposal and rejected the recommendation of every panel that had considered iontophoresis devices. In the final rule, which is still effective today, an iontophoresis device falls in Class II only if

- it is intended to induce sweating for use in the diagnosis of cystic fibrosis, or
- it is intended for use with a drug which bears adequate directions for the device's use with that drug.

At the time, no drug bore labeling with directions for use with an iontophoretic device. A Class III device was, and is, one "intended for any other use." In other words, an iontophoresis device for general drug delivery falls in Class III and requires premarket approval.

3. The Safe Medical Devices Act of 1990

The Safe Medical Devices Act of 1990 (SMDA) added section 515(i) to the FD&C Act. Among other things, this provision required FDA to order the submission of information for preamendment Class III devices not yet subject

³⁶ 48 Fed. Reg. 53032 (November 23, 1983); 21 C.F.R. § 890.5525.

to a call for PMAs, and to reconsider their classification. FDA was to issue a schedule for the call for PMAs within 12 months of publication of any regulation retaining a device in Class III. Also, by December 1995, FDA was either to downclassify preamendment Class III products that had not yet been the subject of a call for PMAs, or to reaffirm their Class III status.

4. Iontophoresis Devices

FDA has not followed the SMDA requirements with respect to preamendment iontophoresis devices meeting the Class III identification. No call for PMAs has issued. FDA has not reconsidered the Class III designation, and the Class III status was not formally reaffirmed after the SMDA. Between May 28, 1976, and August 22, 2000, FDA cleared 41 iontophoresis devices through section 510(k) notification procedures.

FDA now claims that it "discovered" in 1994 that there were no preamendment iontophoresis devices that actually met the Class III identification.³⁷ Since 1994, however, FDA has continued to clear iontophoresis devices through section 510(k) notification procedures. Also, FDA has consistently reminded Class III manufacturers that they may not promote their devices for use with a particular drug unless that drug has been approved for iontophoretic administration.³⁸ That is, FDA has continued to emphasize the

³⁷ 65 Fed. Reg. at 50950.

³⁸ See, e.g., Letter from Lillian J. Gill, Director, Office of Compliance, CDRH, to James R. Weersing, President and Chief Executive Officer, IOMED, Inc. (June 9, 2000); Letter from Lillian J. Gill, Director, Office of Compliance, CDRH, to Alfred C. Coats, President and CEO, Life-Tech, Inc. (February 3, 2000); Letter

distinction between Class II and Class III iontophoresis devices. Until August 22, 2000, the Agency gave no indication that it was reconsidering the classification of iontophoresis devices, the distinction it had established by regulation between Class II and Class III iontophoresis devices, or its view of the history of the devices.

5. The Pending Proposal

FDA now claims that no iontophoresis devices met the Class III definition prior to May 28, 1976. In other words, it claims that prior to May 28, 1976, no iontophoresis devices were marketed for use with drugs the labeling of which did not bear adequate directions for use with the device. Based on this new view of history, FDA proposes to "revise" the Class III identification by eliminating the Class III group of iontophoresis devices.

a. FDA's Notice of Proposed Rule Is Erroneous and Invalid.

As published in the Federal Register, FDA proposes to add subsections (d) and (e) to 21 C.F.R. § 890.5525, without eliminating subsections (a), (b), and (c). This revision would not eliminate the Class III identification. Rather, it would retain the original Class II identification, retain the original Class III identification, and add a second Class II identification. Thus, FDA's notice of proposed rule is inconsistent with the preamble and would fail to

from Douglas C. Payne, District Director, to Alfred C. Coats, CEO/President, Life-Tech Inc. (April 28, 1995) ("Reference to the use of any specific drug with an iontophoretic device requires a new drug application.").

achieve what FDA claims it seeks to accomplish. This notice of proposed rule is erroneous and invalid, and thus unlawful pursuant to 5 U.S.C. § 553(b).

Our comments will nevertheless proceed on the assumption that FDA committed a drafting error and that FDA intends to delete (a), (b), and (c) of section 890.5525, substituting a new (a) and (b).

b. FDA's Proposed Rule Eliminating Class III Identification Is Unlawful.

FDA's proposal would eliminate the Class III identification and require manufacturers of currently marketed Class III devices to conform to the Class II identification. In other words, manufacturers would be required to revise the labeling to limit the use of their devices to administration of pilocarpine. Any manufacturer wishing to market its device for use with another drug would need to ensure that the drug was labeled for iontophoresis; this would require submission of a new drug application (NDA) or abbreviated new drug application.³⁹ No manufacturer would be permitted to continue to manufacture and market a general-purpose iontophoresis device for health care professionals to use as they deem appropriate in the practice of medicine.

³⁹ FDA's decision to require linkage of the device and drug is inconsistent with the 1991 intercenter agreement between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health. That agreement addresses iontophoresis devices, and states that the device and drug in question are "separate entities" -- i.e., not a combination product. According to the intercenter agreement, an iontophoresis device is to be approved or cleared by CDRH separate and apart from any approval by CDER of the drug "unless the intended use of the two products, through labeling, creates a combination product."

II. ARGUMENT

FDA's proposal is based entirely on a single factual premise about which it is clearly wrong. Adoption of this rule would therefore be arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law, in violation of the Administrative Procedure Act, 5 U.S.C. §§ 552 & 706(2). In addition, FDA significantly underestimates the economic impact of its proposal on small businesses like Birch Point, in violation of the Regulatory Flexibility Act, 5 U.S.C. § 601 et seq.

A. FDA Bases Its Proposal on Erroneous Facts.

It is a basic principle of administrative law that an agency decision lacking factual support cannot be sustained. Production Tool Corp. v. Department of Labor, 688 F.2d 1161, 1169 (7th Cir. 1982). It is an abuse of discretion to rely on erroneous factual premises. First Girl Inc. v. Regional Manpower Admin., 499 F.2d 122 (7th Cir. 1974). As explained below, iontophoresis devices have been marketed for Class III uses for decades. FDA's proposal rests entirely on the Agency's bald assertion of an erroneous fact and is an abuse of discretion under the Administrative Procedure Act.

Before May 28, 1976, many companies, including Teca Corporation, Medco Electronics, and Rehabilitation Products, marketed iontophoresis devices that meet the current Class III definition. They were marketed for general drug delivery, and the drugs commonly used did not bear labeling that adequately described iontophoresis. Medical advertisements for iontophoresis devices meeting the current Class III identification from medical

journals dating to the 1950s, 1960s, and 1970s are plentiful. Medical practitioners attest to their use of commercially-marketed iontophoresis devices meeting the current Class III identification during the 1950s, 1960s, and 1970s. And FDA itself has acknowledged that iontophoresis devices meeting the current Class III identification were in widespread use prior to May 28, 1976.

1. Many Companies Marketed Iontophoresis Devices for Class III Uses Prior to May 28, 1976.

We have attached evidence demonstrating that many companies marketed Class III iontophoresis devices meeting the current Class III identification prior to May 28, 1976.

Professional journals prior to May 28, 1976, contained advertisements for iontophoresis devices intended for use with drugs whose labeling did not bear directions for use with the device. For example, attached is an advertisement from the March 1953 issue of Physical Therapy Review for the Teca SP-5 Low Volt and Pulse Generator. Attachment 9. The device was advertised for "ion transfer therapy." This claim of therapeutic use is distinct from a diagnostic use to induce sweating in the diagnosis of cystic fibrosis. Since at least 1939, "ion transfer" has been understood to refer to the use of an electrical current to introduce into the tissue drugs that have been ionized.⁴⁰ Thus, this Teca device advertised for "ion transfer therapy" was marketed for general drug delivery, at the discretion of the treating health care professional.

⁴⁰ See, e.g., AMA Handbook, supra note 1, at 207-08 (discussing "ion transfer" and giving examples of several compounds administered in this way).

Other examples of iontophoresis device promotion for general drug delivery include:

- An advertisement from the January 1954 issue of Physical Therapy Review for the Teca SP-2 offered the device for "ion-transfer therapy." Attachment 10.
- An advertisement for Teca's CD4PS low volt generator appeared in the March 1958 issue of the Physical Therapy Review. Attachment 11.
- Rehabilitation Products advertised its TOMAC MOBILE LOW VOLT GENERATOR in the August 1958 issue of Physical Therapy, for "ion transfer therapy." Attachment 12.
- J.A. Preston advertised its Galvanic-Faradic-Sinusoidal Generator (the PC 1118) in the March 1958 issue of the Physical Therapy Review. Attachment 13.
- J.A. Preston offered its PC 2919 and PC 2900 low volt generators in the August 1963 issue of the Journal of the American Physical Therapy Association. Attachment 1. The "galvanic applications" referenced in the advertisement were iontophoresis procedures.
- Medco Electronics offered its Mark V in the December 1963 issue of the Journal of the American Physical Therapists Association, stating that it was capable of "Medical (D.C.) Galvanism (Iontophoresis)" and explaining that it could be used for "ion transfer." Attachment 14.
- Teca Corporation offered its Model SP5 in the April 1963 issue of the Journal of the American Physical Therapists Association for "ion transfer therapy." Attachment 15.
- Dallons advertised its Medi-Sine Model 1400MGF in the May 1964 issue of Physical Therapy. Although the advertisement does not specify its use for iontophoresis, the "galvanic" function was used for this purpose. Attachment 16.
- Teca Corporation offered its Teca Model SP2 in the September 1964 issue of Physical Therapy for "ion transfer therapy." Attachment 17.

2. Health Care Professionals Used Class III Iontophoresis Devices Prior to May 28, 1976.

As documented in the attachments and summarized in the preceding section, iontophoresis devices were promoted and intended for use in general drug delivery. As shown below, health care professionals used the devices for this purpose. Attached are affidavits from three health care professionals who used iontophoresis devices meeting the current Class III identification prior to May 28, 1976.⁴¹

First, Neil Spielholz used commercially-marketed iontophoresis devices meeting the Class III identification prior to May 28, 1976. Attachment 6. Specifically, he used these devices from 1955 to 1961, while at a Veteran's Administration hospital in Canandaigua, New York, and at a Veteran's Administration hospital in Manhattan, New York. He used iontophoresis to deliver histamine for lower back pain, copper sulfate for athlete's foot, sodium chloride to loosen scar tissue, xylocaine for local pain due to neuromas in amputee stumps and for bursitis, and potassium iodide for venous stasis ulcers. For these treatments, Spielholz used the low volt generators manufactured and marketed by Teca Corporation under the brand names SP2 and CD4. A January 1954 advertisement for the SP2 is Attachment 10 to these comments; a March 1958 advertisement for the CD4 is Attachment 11; a September 1964 advertisement for the SP2 is Attachment 17.

⁴¹ These affidavits conform to FDA's guidance entitled "Documentation Required for Preamendment Status" (December 24, 1997).

Second, Luther Kloth used commercially-marketed iontophoresis devices meeting the Class III identification prior to May 28, 1976. Attachment 4. Kloth learned physical therapy at the University of Pennsylvania in the 1960s, and was taught to use iontophoresis for clinical treatment of musculoskeletal calcium deposits (acetic acid), for pain suppression (histamine), for fungal infections (copper sulfate), for musculoskeletal inflammatory conditions (sodium salicylate and/or mecholyl), for analgesia (novocaine), and for edema reduction (hyaluronidase). Between 1962 and 1965, he used a commercially-marketed TECA SP5 for iontophoresis of these drugs for these purposes at the Lankenau Hospital in Philadelphia and at the Maine Medical Center in Portland. An April 1963 advertisement for the SP5 is Attachment 15 to these comments. The labeling and promotion for the TECA SP5 did not reference any particular drug or medical condition, and to his knowledge none of the drugs he used was labeled for delivery via iontophoresis.

Third, Danny D. Smith used commercially-marketed iontophoresis devices meeting the Class III identification prior to May 28, 1976. At the University of Tennessee in 1971, Smith was taught to administer lidocaine, dexamethasone, and acetic acid for the treatment of bursitis, tendonitis, plantar fasciitis, scar tissue, and various forms of arthritis. In practice, he used a Mettler DC Generator with these drugs for these purposes. The labeling and promotion of the device did not reference any particular drug or condition. None of the drugs that he used was labeled for iontophoresis.

3. FDA Has Acknowledged that Class III Iontophoresis Devices Were in Widespread Use Prior to May 28, 1976.

FDA's writings in 1979 and 1983 concede that iontophoresis devices meeting the Class III identification were marketed prior to the Medical Device Amendments. FDA wrote in 1979 that "the use of fluoride iontophoresis has a broad application in dental practice."⁴² FDA discussed and proposed to place into Class II iontophoresis devices for (a) the application of fluoride to the teeth, and (b) the introduction of lidocaine and epinephrine into the tympanic membrane of the ear in order to anesthetize.⁴³ FDA cited fourteen journal articles on iontophoresis, nine of which predate 1976, and quoted a 1967 article that "iontophoresis has been widely used in clinical practice for many years."⁴⁴ In 1983, FDA admitted that it was "unaware of any marketed drug that has labeling providing adequate directions for its use with an iontophoresis device for the dental application of fluoride or the anesthetizing of the intact tympanic membrane."⁴⁵ In other words, FDA acknowledged the fact that the iontophoresis devices were and had been widely marketed for and used with precisely these drugs for precisely these indications. FDA also acknowledged that no drugs were labeled for use with these devices. It is simply wrong for FDA to write, in 2000, that there were no iontophoresis devices prior to May 1976 intended for use with drugs whose labeling did not bear adequate directions for use with

⁴² 44 Fed. Reg. at 50522.

⁴³ Id. at 50522-50523.

⁴⁴ Id. at 50521.

⁴⁵ 48 Fed. Reg. at 53045.

those devices.⁴⁶ It defies common sense that FDA would publish a Federal Register proposal so plainly at odds with the Agency's own prior statements.

In addition, at two advisory committee meetings in 1978, which FDA convened and which FDA staff attended, it was made clear that clinicians had used commercially-marketed iontophoresis devices with drugs for years. At the July 1978 meeting of the Physical Medicine Device Classification Panel, Keith B. Sperling, chairman of the panel and Director of the Minneapolis Spinal Cord Injury Center at the University of Minnesota, commented that when he "came into" the field, he "used [iontophoresis] probably twenty times." (Tr. 126.) As to whether the device was used more commonly in plastic surgery or physical medicine, Dr. Justis Lehman (Professor and Chairman of the Department of Rehabilitation Medicine at the University of Washington Hospital in Seattle) stated that it is "used most frequently in the area of competence of this panel" but "we have sporadically scattered usage everywhere." (Tr. 126.) Dr. Lehman read to the panel a statement that "Iontophoresis has been widely used in clinical practice for many years." (Tr. 128.) He later added that "When I went to Seattle, everyone in town was doing iontophoresis." (Tr. 137.) A Mr. Lipsky commented that "there are seven companies that just entered the market." (Tr. 136.) Most significantly, the panel was aware that the drugs used with iontophoresis devices were in fact approved for other uses. Dr. Lehmann commented, on closing:

⁴⁶ 65 Fed. Reg. at 50950.

"The equipment performs fine, and the drug end is a different story, but you see the drugs are approved in other contexts." (Tr. 147.)

At the November 1978 meeting of the Ear, Nose, and Throat Device Classification Panel, David J. Anderson, a panel member, inquired about the control of current on "devices that are on the market right now." (Tr. 19.) Robert Brummett, a speaker, confirmed that "the device is being marketed, yes." (Tr. 19.) "The device is being marketed by Xomed," he added. (Tr. 19.) "Iontophoresis, of course, is something that's not patentable. It's been around for years." (Tr. 20.) Panel member Martha Rubin asked "Is there more than one device?"; Brummett responded "There are other devices on the market, yes." (Tr. 20.) Panel member Roy K. Sedge asked "How long have they been marketed commercially?"; Don Bruce, who represented a manufacturer, responded that "Xomed has been marketing this one for at least four years" (i.e., since at least 1974). (Tr. 20.)

At the advisory committee meeting in 1979, between publication of the proposed rule and publication of the final rule, it was again made clear that clinicians had been using iontophoresis devices for general drug delivery for decades. Dr. Arnold, a guest of the Physical Medicine Section of the Surgical and Rehabilitation Devices Panel observed that "historically in physical medicine 25 or 30 years ago [i.e., in the 1950s] there was much more use of iontophoresis for 'delivery of medicine' than there is now." (Tr. 19.)

4. Preamendment Literature Documents Clinical Use of Iontophoresis Devices Meeting the Class III Identification.

A significant amount of secondary literature dating to the preamendment period also confirms the marketing and use of iontophoresis devices for general drug delivery.

For instance, in 1937, H. Abramson and A. Alley wrote in the Archives of Physical Therapy, X-Ray, Radium that "the introduction of histamine into the skin by a direct electric current is a therapeutic measure in widespread use."⁴⁷ The same issue of the Archives also included the abstract of an article in the Journal of the Arkansas Medical Society discussing the clinical use of iontophoresis for treatment of allergic diseases in the nose.⁴⁸

In the February 1938 issue of the New York State Journal of Medicine, Dr. Karl Harpuder wrote that "Electrophoresis -- also called iontophoresis or ionization -- has been used extensively as a therapeutic method during the last decade. It consists of the application of the galvanic current to carry into the skin or into mucous membranes, substances which would otherwise penetrate to a much lower degree or not at all. . . . [I]ts therapeutic

⁴⁷ H. Abramson et al., "Skin Reactions. I. Mechanism of Histamine Iontophoresis from Aqueous Media," Archives of Physical Therapy, X-Ray, Radium 18: 327 (June 1937) (Attachment 18).

⁴⁸ V. Payne. "My Results with Ionization Treatment in Nasal Allergy," Archives of Physical Therapy, X-Ray, Radium 18: 598 (September 1937) ("Iontophoresis is the best therapeutic agent that the otolaryngologist possesses for the treatment of allergic diseases of the nose.") (Attachment 19).

usefulness has more recently been shown with the application of histamine and of choline compounds."⁴⁹

The June 1977 issue of Physical Therapy contained an article on acetic acid iontophoresis for calcium deposits in its regular Suggestion from the Field column. Dr. Kahn wrote that "[i]ontophoresis with acetic acid has been my standard approach to the treatment of calcium deposits for about 25 years."⁵⁰ In addition to providing directions for such treatment, Dr. Kahn suggested using the Teca Corporation SP2, a device manufactured and marketed for ion transfer therapy as early as 1954. A January 1954 advertisement for the SP2 is Attachment 10 to these comments.

Finally, trade press demonstrates the preamendment marketing of iontophoresis devices meeting the Class III identification. For instance, when the Ear, Nose, and Throat Panel voted in November 1978 to place iontophoresis devices for the delivery of epinephrine and lidocaine into the inner ear into Class II, one industry paper noted that the device in question had been "marketed since 1974."⁵¹

* * *

In sum, iontophoresis devices were commercially-marketed in interstate commerce for general drug delivery as early as 1953. Attachment 9.

⁴⁹ K. Harpuder, "Electrophoretic Therapy: Problems and Value," N.Y. State Jour. of Medicine 38/3: 176 (February 1938) (Attachment 20).

⁵⁰ J. Kahn, "Acetic Acid Iontophoresis for Calcium Deposits," Physical Therapy 57/6: 658 (June 1977) (Attachment 21).

⁵¹ M-D-D-I Reports, November 13, 1978, at 2 (Attachment 22).

— They were marketed for use in general drug delivery at the discretion of the health care professional -- both before the 1962 Drug Amendments, Attachment 12, and after the 1962 Drug Amendments, Attachment 15. They were used by health care professionals prior to May 28, 1976, for treatment of a wide variety of ailments with a wide variety of drugs. Attachments 4, 6, 7. To the best of our knowledge, between 1962 and December 21, 1995, no drug was labeled for administration via iontophoresis.

B. FDA Underestimates the Economic Impact of its Proposal on Small Businesses, in Violation of the Regulatory Flexibility Act, 5 U.S.C. § 601 et seq.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities.⁵² In particular, an agency must consider the impact of its proposal on small business entities. It must consider alternatives to its proposal that would be less burdensome, unless it certifies that the rule will not have a "significant economic impact" on a "substantial number of small entities."

1. FDA Did Not Adequately Support its Certification that the Proposal Would Not Have a "Significant Economic Impact" on a "Substantial Number of Small Entities."

In its proposal, FDA certifies that its proposal would not have a significant economic impact on a substantial number of small entities. However, the Agency's analysis is cursory and starts from the wrong premise.

⁵² 5 U.S.C. §§ 601-612, as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996, Pub. L. No. 104-121.

When an agency certifies that a rule will not "have a significant economic impact on a substantial number of small entities," the agency must provide "the factual basis for such certification."⁵³ Certification is not merely a procedural step that an agency can satisfy with boilerplate language. Congress expects an agency to explain how its conclusion was reached.⁵⁴

FDA devotes one paragraph to its conclusion that the economic impact of its proposal would be "minimal." FDA writes that "21 manufacturers have 41 510(k)s that will be affected by this proposed rule."⁵⁵ In the Agency's view, compliance with its proposal "will involve only changes in device labeling in the existing 510(k)s" and preparation of these changes "will require minimal cost."⁵⁶ FDA concludes that "the cost of complying with the labeling requirements for each manufacturer will be approximately \$1,000."⁵⁷ Accordingly, FDA chose to "certify" the lack of a significant economic impact, and dispense with any inquiry into less burdensome alternatives.

FDA's cursory analysis starts from the wrong premise. It starts from the premise that FDA has simply proposed to require a change in the

⁵³ 5 U.S.C. § 605(b).

⁵⁴ See H.R. Rep. No. 104-48, at 8 (1995) ("Debate during floor consideration indicated that this [required] explanation should be more than a mere statement that a rule will not have a significant impact on a substantial number of small entities. It must explain the decision to certify and discuss why it draws that conclusion, and any doubt as to whether an impact analysis should be filed must be resolved in favor of performing the analysis.")

⁵⁵ 65 Fed. Reg. at 50951.

⁵⁶ Id.

⁵⁷ Id.

labeling of marketed devices. This is belied by its own subsequent suggestion that the proposal is really a "reclassification" proposal. FDA writes that "Reclassification of the device from Class III into Class II will relieve manufacturers of the cost of complying with the premarket approval requirements in section 515 of the act."⁵⁸ This statement ignores the fact that devices currently in Class III will not be "reclassified" into Class II. Instead, they will be banned from the market.

In truth, FDA's proposal is neither a labeling change nor a reclassification proceeding. FDA proposes to eliminate from the market, outright, iontophoresis devices that meet the current Class III designation. As explained below, there is a \$38.7 million industry in Class III iontophoresis devices.

Elimination of this market will entail costs to small business entities -- including Birch Point -- vastly exceeding \$1,000 per entity.

2. There is a \$38.7 Million Industry in Class III Iontophoresis Devices.

The total annual revenue in the United States derived from iontophoresis (Class II and Class III) approximates \$40 million.⁵⁹

Class II iontophoresis devices are iontophoresis devices
(1) intended for use with pilocarpine for diagnosis of cystic fibrosis, or
(2) intended for use with a specific drug labeled for delivery through

⁵⁸ Id.

⁵⁹ In its 10-K filing at the SEC for the fiscal year ending June 30, 2000, Iomed estimated the present retail sales in the iontophoresis market to be approximately \$40 million. Attachment 23.

iontophoresis. Although this number is necessarily an educated guess, we believe Class II procedures account for \$1.3 million of the annual market in iontophoresis. Approximately 100,000 pilocarpine procedures are performed annually, generating an estimated \$1 million in revenue.⁶⁰ Only one therapeutic drug bears labeling for use with an iontophoresis device -- Iontocaine. We estimate that revenue from Iontocaine iontophoresis may approximate \$300,000 per year.⁶¹

Class III devices are general iontophoresis devices, marketed for ion transfer therapy and not intended for use with any particular drug. They are used by health care professionals to administer the drugs they choose, according to their own best professional judgment. The remaining \$38.7 million of the annual market consists of Class III iontophoresis devices.

3. The Cost of Eliminating this Market Will Exceed \$1000 per Manufacturer.

Elimination of this \$38.7 million dollar industry will affect primarily small business entities. A "small business entity" in the surgical and medical instrument manufacturing industry is one with 500 or fewer employees.⁶² Birch

⁶⁰ According to the Cystic Fibrosis Foundation, approximately 1000 new cases of cystic fibrosis are diagnosed via sweat test each year. We estimate a 100 to 1 ratio of tests to positive diagnoses, and we are aware that the test costs approximately \$10. Thus, we estimate pilocarpine procedures could generate as much as \$1 million per year.

⁶¹ This number is based on communication with a number of knowledgeable industry sources. Although we can provide no documentation to support this number, Iomed's June 2000 filing at the SEC states that its combination product, to date, "has not generated significant revenues." Attachment 23.

⁶² The Regulatory Flexibility Act provides that "small business entity" has "the same meaning as the term 'small business concern' under section 3 of

Point is a "small business entity" because it has fewer than a dozen employees. Indeed, we estimate that of the 24 manufacturers of marketed Class III devices, 23 are small business entities.

The 23 small business manufacturers that market Class III iontophoresis devices will be unable to market those devices if FDA finalizes its proposal. Each small company, including Birch Point, will have two choices: (1) to abandon the general iontophoresis market and market solely for cystic fibrosis diagnosis; or (2) to seek a change in the labeling of other drugs through the new drug application procedures and to submit a section 510(k) notification, in order to market its device for use with that drug.

Either option will cost a manufacturer more than \$1000. As to the first choice, FDA may be correct that the manufacturer can print and use new labels conforming to the Class II identification. However, FDA failed to consider the cost to each Class III device manufacturer of abandoning Class III sales. The cost of abandoning the \$38.7 million Class III market will cost more than \$1 million per company. Birch Point had projected its revenues from Class III marketing to reach \$70 million over the next five years. Moreover, the market for cystic fibrosis tests and iontophoresis administration is a limited market. Not all Class III manufacturers would survive. As to the second option, if a manufacturer

the Small Business Act." 5 U.S.C. § 6013). The Small Business Act directs the Small Business Administration (SBA) to set standards to determine whether a business is a "small business concern." 15 U.S.C. § 632(a). The SBA has stated that in the surgical and medical instrument manufacturing sector, a business with 500 or fewer employees is a small business. 65 Fed. Reg. 53533, 53546 (September 5, 2000) (to be codified at 13 C.F.R. Part 121).

— of a Class III device were to seek a change in the labeling of a drug through the new drug application process, clinical trials alone for each drug could cost several million dollars.

Birch Point in particular will be crippled if FDA finalizes its proposal. Birch Point obtained 510(k) clearance for its Class III IontoPatch on February 1, 2000. Birch Point invested over \$1 million in development of the IontoPatch.

Sales of the product have just begun. As representatives of Birch Point explained to FDA staff in December 1999, the company's long-range business plan requires a period of Class III marketing in order to (a) recoup the research and development investment and (b) generate adequate revenue to support clinical trials for a supplemental NDA for a drug that we believe can be

— administered via iontophoresis and should be labeled for that administration.

Phase 1 of our business strategy involves introduction of the IontoPatch into the general physical medicine market under the Class III identification. Phase 2 will entail marketing the IontoPatch as an integrated drug delivery system (after approval of an NDA). A contract research organization that may design and conduct the clinical trial in question has estimated that a trial similar to the one conducted by Iomed for Iontocaine would cost us several million dollars. In short, a period of Class III marketing is essential to the Birch Point business model.

FDA is surely aware that device manufacturers tend to be small business entities without the capital to support drug clinical trials. Eliminating the Class III market will prevent many device manufacturers from developing the data necessary for Class II designation. It will foreclose future clinical research

on these devices, and ultimately narrow the therapeutic options for patients. It will substantially interfere with the practice of medicine.

It defies common sense for FDA to certify that banning from the market a device marketed by 23 small business entities will not have a "significant economic impact on a substantial number of small entities." FDA must therefore consider alternatives which would minimize this economic impact and still accomplish its objectives. Indeed, Congress made clear in 1995 that this analysis is the most important requirement of the Regulatory Flexibility Act.⁶³ Congress affirmed its intent to emphasize this requirement in 1996 by amending the Act to allow judicial review of certifications and of an agency's final regulatory flexibility analysis.⁶⁴

In sum, FDA's failure to conduct an economic analysis in connection with this proposed rule violates the Regulatory Flexibility Act.

III. CONCLUSION

As discussed above and established by evidence accompanying these comments, iontophoresis devices meeting the Class III identification were marketed prior to May 28, 1976. FDA is trying to rewrite history by asserting, in this proposal, that there were no preamendment devices meeting the Class III identification. Since FDA is plainly wrong about the only "fact" on which its proposed rule is based, the proposed rule is arbitrary, capricious, an abuse of discretion, and otherwise not in accordance with law. FDA has also violated the

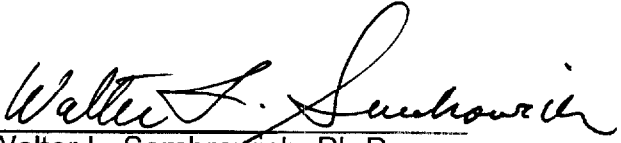
⁶³ H.R. Rep. No. 104-49, pt. 1, at 7 (1995).

Regulatory Flexibility Act, in that the Agency's analysis and certification of a lack of significant economic impact is based on the erroneous assertion that the rule would require a simple change in labeling, and thus grossly underestimates the impact on small business entities.

For the foregoing reasons, FDA must withdraw the current proposal.

Respectfully submitted,

December 14, 2000


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⁶⁴ 5 U.S.C. § 611(a)(1).

ATTACHMENTS

1. Advertisement: PC 2918, 2919, 2900, 2901 (1963)
2. American Medical Association, Handbook of Physical Therapy (3d ed. 1939)
3. Linda Amrein et al., "Use of Low Voltage Electrotherapy and Electromyography in Physical Therapy," Physical Therapy 51/12: 1283 (1971).
4. Affidavit of Luther C. Kloth
5. Joseph Kahn, Principles and Practice of Electrotherapy (1987) (excerpt)
6. Affidavit of Neil I. Spielholz
7. Affidavit of Danny D. Smith
8. Merck Brochure for Mecholyl (1941)
9. Advertisement: TECA SP-5 (1953)
10. Advertisement: TECA SP-2 (1954)
11. Advertisement: TECA CD4 P5 (1958)
12. Advertisement: TOMAC (1958)
13. Advertisement: PC 1118, PC 1120 (1958)
14. Advertisement: MARK V (1963)
15. Advertisement: TECA SP-5 (1963)
16. Advertisement: DALLONS 1400MG (1964)
17. Advertisement: TECA SP-2 (1964)
18. Abramson et al., "Skin Reactions. I. Mechanism of Histamine Iontophoresis from Aqueous Media," Archives of Physical Therapy, X-Ray, Radium 18: 327 (June 1937).
19. V. Payne. "My Results with Ionization Treatment in Nasal Allergy," Archives of Physical Therapy, X-Ray, Radium 18: 598 (September 1937)
20. K. Harpuder, "Electrophoretic Therapy: Problems and Value," N.Y. State Jour. of Medicine 38/3: 176 (February 1938).

21. J. Kahn, "Acetic Acid Iontophoresis for Calcium Deposits," Physical Therapy 57/6: 658 (June 1977).
22. M-D-D-I Reports (November 13, 1978), at 2.
23. Iomed 10-K (June 30, 2000) (excerpts).